REMARKS / ARGUMENTS

Upon entry of this amendment, the claims pending are claims 1-17, 24-26, and 28-43. Claims 18-23 were cancelled by previous amendments. These claims stand canceled without prejudice to refiling as non-elected subject matter. Claim 27 is canceled herein.

Claims 1, 2, 4-9, 11, 12, 15-17, 24, 26, 28, 30-35, 37, 38, 41 and 42 are amended to clarify the invention, to correct grammatical errors and to comply with §112, second paragraph, as specified below. Claim 43 is new and is supported by original claim 27. The specification is amended to correct the volume, pages and year of a citation on page 116. No new matter was added by these amendments, which are supported in the original specification and by the original claims.

Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of the non-elected claims.

Claim Objections

Claim 24 is objected to because of the use of "encode" instead of --encodes--.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendment to Claim 24 correcting the noted grammatical error.

Claim Rejections based on 35 USC §101

> Claim 27 is rejected because the recitation of a use, without any steps is an allegedly improper definition of a process.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above cancellation of Claim 27. New claim 43 is free of this rejection because it provides a method for preparing an antigenic composition containing the step of combining the mutant cholera holotoxin with a selected antigen. This amendment satisfies and renders moot this ground of rejection.

Claim Rejections based on 35 USC §112, first paragraph

> Claims 12 and 38 are rejected as allegedly containing subject matter not described in the specification in such a way as to show possession of the claimed invention. Specifically, the examiner states that the plasmid DNA encoding HSV gD2 antigen has not been described and a deposit is required.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Claims 12 and 28 do not require the use of any specific plasmid, merely ***a*** plasmid encoding HSV gD2. Such plasmids were available in the prior art as of the filing date of this application. For example, an exemplary plasmid DNA encoding HSV gD2 was described by the publication Pachuk, C. *et al*, **1998** *Curr. Topics Microbiol. Immunol.,* 226:79-90. This publication was made prior to the September 30, 1998 priority date to which this application is entitled. This publication was referenced in Example 13 at pp. 109-113 of the instant specification, but the citation on page 116 contained the incorrect volume and date. However, one of skill in the art could readily locate the correct citation using the correct author and volume and subject matter. Further, such an exemplary plasmid was known to the prior art by its description in the publication of International Patent Publication No. WO 98/17820 on April 30, 1998, which was prior to the September 30, 1998 priority filing date to which this application is entitled. Still other exemplary HSV gD2 plasmids were described by others in the prior art before the priority filing date of this application. See e.g., Nicola *et al.*, **2996** *J. Virol., 70*:3518-3822..

Applicants respectfully submit that the specification, citing the Pachuk *et al* publication as an example, as well as the presence of earlier publications in the prior art are sufficient to describe an exemplary HSV gD2 plasmid for the purposes of this application. No additional deposits or descriptive material should be necessary to enable Claims 12 or 28.

Thus, this rejection may be properly withdrawn.

Claim Rejections based on 35 USC §112, second paragraph

> Claims 1-17 and 24-42 are rejected under 35 USC §112, second paragraph, for alleged indefiniteness in view of lack of a reference sequence for the position numbers in the claims. Claim 1 is said to define a single antigen due to the phrase "a selected antigen". Therefore Claim 2 is found to be indefinite in "comprising more than one antigen". Claims 3 and 29 lack antecedent basis for use of the phrase

> "amino acid". Claims 5, 31 and 7, 33 lack antecedent basis for the terms "combination". Claims 12 and 28 do not find antecedent basis for "polynucleotide" and require clarification as to the antigenic compositions and vaccine contents. Claims 14 and 40 comprise an additional adjuvant but it is not clear that Claim 1 requires the mutant cholera holotoxin. Claims 15 and 41 do not require the mutant to evidence adjuvant activity. Claims 16 and 42 define a molecule of any size due to any mutation introduced into the A subunit. Claim 26 uses "protein" which lacks antecedent basis, and omits essential steps, e.g., expressing the holotoxin and recovering it. Claim 27 lacks specific methods steps.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Regarding the identity of the amino acid position numbers, Applicants draw the examiner's attention to the document cited by the specification, i.e., Mekalanos *et al*, **1983** *Nature*, 306:551-557, (as "Bibliography entry 1" on page 2, lines 3-4 and as the first citation on page 114, labeled "Bibliography"). This reference is the standard reference in the art for the well-known sequence of cholera toxin and its subunits. Such sequences are also available in the NCBI database, as submitted by the authors of the above-noted publication. Thus, in publications throughout the art, a reference to position 29 of wild-type cholera toxin subunit A is understood by those of skill in the art to mean the highlighted amino acid in the well-known sequence of subunit A from that 1983 reference (set out below). Note that in a variety of publications, the authors use the same convention for identifying amino acid positions of cholera toxin subunit A, i.e., by identifying the amino acid by position number with a reference to the Mekalanos et al publication. Such publications did not feel it necessary to set out the well-known sequence. See, e.g., International Publication Nos. WO 97/02348 and WO 97/29771 and background references cited therein; and Vadheim K.L, *et al*, **1994** *Microb. Pathog., 17*(5):339-46.

For this reason, Applicants do not believe that a sequence identifier is necessary to make definite the amino acid positions identified by the claim language. One of skill in the art would recognize the meaning of the amino acid positions based on the current claim language.

The additional amendments to Claim 1 are made to insert appropriate Markush language, insert language providing antecedent bases for the dependent claims (e.g., "amino acid", "at least one", and the polynucleotide sequence language), and correct any

grammatical errors. Thus, the amendments to Claim 1 make clear that the mutant cholera holotoxin (present as a second component, either as a protein or as a polynucleotide sequence encoding the protein for subsequent expression in a host cell) is an essential component of the composition. This has the effect of obviating, on this basis alone, many of the examiner's prior art rejections, as will be discussed below.

Amendments to Claims 2, 4-9, 11 and 17 are minor and made to conform antecedent basis and/or correct Markush group language. The addition of "amino acid" in Claim 1 removes the grounds for rejection of Claim 3.

Claim 12 is amended to conform its language with the amended language of Claim 1. The amendment of Claim 1 also removes the rejection of Claim 14.

Claim 15 is amended to clarify the language by restating that the mutant with the additional mutation also enhances the immune response (i.e., operates as an adjuvant).

With regard to the examiner's concern about Claims 16 and 42, Applicants have amended the claim to specify clearly what that the substitutions are for an amino acid of the subunit and to specify the precise substitutions in a Markush group. Even if one were to include all of the additional mutations, one would obtain a mutant cholera holotoxin subunit A of an expected size, containing one or more of those amino acid substitutions. These amendments are believed to satisfy this ground for rejection.

Claim 24 is amended to correct grammatical errors and clarify the claim language by inserting the terms "amino acid" and "wild-type". Claim 26 is amended to correct reference to the holotoxin, thereby conforming it with the language of Claim 1 and by adding the "missing" steps of the process.

Amendments to Claims 28-42 parallel the amendments to claims 2-26.

New Claim 43 is supported by cancelled Claim 27 and presents the claim in method format with the step of combining.

In view of the above amendments to the claims, this rejection is satisfied and may be withdrawn as against all pending claims.

Claim Rejections based on 35 USC §102(b)

A. Claims 1, 2, 4, 6, 11, 13, 17, 28, 30, 32, 37-39 are rejected under Section 102(b) as allegedly anticipated by International Patent Application Publication No. WO95/17211 (Rappuoli).

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Rappuoli refers to immunogenic compositions comprising an immunologically effective amount of an antigen and a mucosal adjuvant. Rappuoli refers to an *E. coli* labile toxin (LT) mutant having a Glu-Lys mutation at position 112, which was inactive as an adjuvant, and a mutant LT with and Arg to Lys substitution at position 7. Rappuoli also refers to a pertussis toxin (PT) mutated at position 129 with a Glu to Gly mutation, or a mutant LT with a Arg-Gly substitution at position 192. Rappuoli refers generally to detoxified mutants of cholera toxin. However, nowhere in Rappuoli is there any reference to cholera toxin subunit A with a mutation at position 29. The antigenic compositions described therein do **not** require the presence of a mutant cholera holotoxin with a substitution at position 29.

In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

B. Claims 1, 2, 4, 5, 13, 17, 28, 30-31 and 39 are rejected under Section 102(e) as allegedly anticipated by U.S. Patent No. 6,245,337 (St. Geme III). The examiner states that St. Geme III anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

St. Geme III refers to antigenic compositions containing *H. influenzae* antigens, optionally in combination with unspecified adjuvants. Nowhere in St. Geme III is there any reference to cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

C. Claims 1, 2, 11-13, 17, 28, 30 and 37-39 are rejected under Section 102(b) as allegedly anticipated by U.S. Patent No. 5,171,568 (Burke). The examiner states Burke anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Burke refers to antigenic compositions containing Herpes Simplex virus antigens, gB or gD, optionally in combination with a variety of adjuvants. Nowhere in Burke is there any reference to cholera toxin adjuvant, much less an adjuvant which is a cholera toxin with a mutant subunit A. There is no disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

D. Claims 1, 2, 4, 6, 13, 17, 28, 30, 32 and 39 are rejected under Section 102(e) as allegedly anticipated by U.S. Patent No. 5,972,336 (Michetti I). The examiner states that Michetti I anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Michetti I refers to antigenic compositions containing *Heliocobacter* subunit urease or urease subunits as antigens, optionally in combination with a variety of adjuvants. Michetti I refers to oral immunization of mice with purified *H. pylori* urease and administering cholera toxin (Sigma) as a mucosal adjuvant (col. 6-7; col. 13, line 49 et seq.). Note that Rappuoli above noted that cholera toxin was a useful mucosal adjuvant in mice, but was toxic in humans in its wild-type form. Michetti I does not address this point. Nowhere in Michetti I is there any reference to a *mutant* cholera toxin adjuvant, much less an adjuvant which is a cholera toxin with a mutant subunit A. There is ***no*** disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

E. Claims 1, 2, 4, 6, 9, 13, 17, 28, 30, 32 and 39 are rejected under Section 102(e) as allegedly anticipated by U.S. Patent No. 6,290,962 (Michetti II). The examiner states that Michetti II anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Michetti II refers to antigenic compositions containing *Heliocobacter* subunit urease or urease subunits as antigens, optionally in combination with a variety of adjuvants. Michetti II refers to immunization of *H. pylori* urease in association with a mucosal adjuvant, such as the B subunit of cholera toxin (col. 8, lines 52-55). Michetti II refers generally to non-toxic derivatives of cholera toxin, its subunit B, or conjugates or fusions of urease with cholera toxin or its B subunit (col. 9, lines 17-21; col. 12, lines 37-45). Nowhere in Michetti II is there any reference to a cholera toxin subunit A adjuvant, much less a *mutant* cholera toxin subunit A adjuvant. There is ***no*** disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

F. Claims 1, 2, 4, 9-10, 13, 17, 28, 30, and 35-36 are rejected under Section 102(a) as allegedly anticipated by O'Neal *et al* **1998** *J. Virol., 72*(4):3390-3393. The examiner states that O'Neal anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

O'Neal refers to antigenic compositions containing rotavirus 2/6 virus-like particles administered intranasally to mice with cholera toxin and other adjuvants. O'Neal noted that "it is unclear whether CT will be approved for human use.." (page 3390, abstract). O'Neal noted that a number of mutants of CT have been developed, citing Yamamoto *et al*, **1997** *J. Exp. Med.*, 185:1203-1210. However, nowhere in O'Neal is there any reference to a cholera toxin subunit A adjuvant, much less a *mutant* cholera toxin subunit A adjuvant. There is ***no*** disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

G. Claims 1, 2, 4, 7, 13, 17, 28, 30, 33 and 39 are rejected under Section 102(e) as allegedly anticipated by U. S. Patent No. 6,558,677 (Zollinger). The

examiner states that Zollinger anticipates the antigenic compositions that do *not* require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Zolinger refers to antigenic compositions containing *Neisseria* outer membrane vesicles as antigens. Nowhere in Zollinger is there any reference to a cholera toxin adjuvant, or an adjuvant which is a cholera toxin with a *mutant* subunit A. There is ***no*** disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

H. Claims 1, 2, 4, 7, 13, 17, 28, 30, 33 and 39 are rejected under Section 102(e) as allegedly anticipated by U. S. Patent No. 6,395,964 (Arntzen). The examiner states that Arntzen anticipates the antigenic compositions that do *not* require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Arntzen refers to antigenic compositions produced in transgenic plants expressing bacterial antigens that act as both immunogen and adjuvant. Arntzen refers to cholera holotoxin or subunits containing replacement codons to facilitate plant transcription through the replacement of bacterial A and T-rich preferred amino acid codons for plant preferred amino acid codons for use in this method (col. 12, lines 49-55; col. 18, lines 23-34). Embodiments of Arntzen's vaccines can contain sequences encoding components of cholera toxin subunit A (col. 14, lines 12-13) and/or other non-cholera toxin antigens. However, nowhere in Arntzen is there any disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. Further, while Arntzen suggests the use of subunit B as an adjuvant, he appears to refer to subunit A as useful to reassemble the intact toxin when co-expressed with subunit B. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

I. Claims 1, 2, 4-8, 13, 17, 28, 30-34 and 39 are rejected under Section 102(e) as allegedly anticipated by U. S. Patent No. 6,514,503 (Gizurarson). The examiner states that Gizurarson anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Gizurarson refers to compositions comprising any of a variety of antigens (col. 6) and a mucosal adjuvant containing 0.01 – 70% v/v of glycerides of a particular formula (see col. 3). Additional conventional adjuvants may also be added to this composition (col. 11), including bacterial toxins as carriers. Nowhere in Gizurarson is there any reference to cholera toxin adjuvant, much less an adjuvant, which is a cholera toxin with a mutant subunit A. There is no disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

J. Claims 1, 2, 4-8, 13, 17, 28, 30-34 and 39 are rejected under Section 102(e) as allegedly anticipated by U. S. Patent No. 5,679,352 (Chong). The examiner states that Chong anticipates the antigenic compositions that do ***not*** require the presence of a mutant holotoxin with a substitution at position 29.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks.

Chong refers to a synthetic *H. influenzae* conjugate vaccine linked to a carrier molecule, particularly a synthetic polyriboxylribitol phosphate (PRP) molecule or polymerized form. Nowhere in Chong is there any reference to a cholera toxin adjuvant, much less an adjuvant which is a cholera toxin with a mutant subunit A. There is no disclosure or suggestion of a cholera toxin subunit A with a mutation at position 29. In view of the above amendments that require the presence of a mutant holotoxin with a substitution at position 29 in all of Applicants' claims, this rejection may be properly withdrawn.

With regard to the rejections set out in paragraphs A-I above, Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the above amendments to the claims and the following remarks. The examiner cites all of these

references as anticipating the identified claims, but acknowledges that the antigenic compositions described therein do **not** require the presence of a mutant holotoxin with a substitution at position 29. As amended, the pending claims clarify that the presence of a mutant holotoxin with a substitution at position 29 is always **required**. Thus, all grounds for rejection in paragraphs A through I may be properly withdrawn.

Miscellaneous

Applicants respectfully draw to the examiner's attention that the Form 1449 from the first Information Disclosure Statement (IDS), filed on October 3, 2001, in the above-identified application was not attached with the examiner's initials and date of consideration. Following a telephone conference on October 7, 2003 with Examiner Portner, it appears that this first IDS never reached the examiner. Therefore, Applicants are attaching to this response a second copy of that IDS and Form 1449, with a copy of the USPTO stamped postcard receipt. Applicants are also attaching copies of the documents cited in that first IDS that are not also cited by the Examiner to ensure that all documents are considered.

Additionally, attached hereto is a Second Supplemental IDS listing a document that was cited in the corresponding Australian patent application.

Applicants request that the examiner consider these documents and initial and date the Forms 1449 appended thereto.

In view of the above claim amendments and remarks, Applicants respectfully submit that the claim rejections have been overcome and that the present application is in condition for allowance. Accordingly, allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment for entering this Amendment to our deposit account no. 08-3040.

Respectfully submitted,
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